

Histological variability and the importance of clinicopathological correlation in cutaneous Rosai-Dorfman disease*

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Abstract: Rosai-Dorfman disease is a benign histiocytic proliferative disorder of unknown etiology. The disease mainly affects lymph node tissue, although it is rarely confined to the skin. Here, we describe a 53-year-old woman with purely cutaneous Rosai-Dorfman disease. The patient presented with a large pigmented plaque on her left leg, and sparse erythematous papules on her face and arms. A complete clinical response was achieved with thalidomide, followed by recurrence at the initial site one year later. The histological examination displayed the typical features of Rosai-Dorfman disease in the recent lesions but not in the older lesions. In the setting of no lymphadenopathy, the histopathological features of Rosai-Dorfman disease are commonly misinterpreted. Therefore, awareness of the histological aspects present at different stages, not always featuring the hallmark microscopic signs of Rosai-Dorfman disease, is particularly important for a correct diagnosis of this rare disorder.

Keywords: Emperipolesis; Histiocytosis; Histiocytosis, sinus; Thalidomide.

INTRODUCTION

Rosai-Dorfman disease (RDD) is a benign histiocytic proliferative disorder of unknown etiology. Typically, it presents as a painless, bilateral, massive, cervical lymphadenopathy, commonly in association with systemic symptoms, such as fever, weight loss, night sweats, leukocytosis, polyclonal gammopathy and increased erythrocyte sedimentation rate (ESR).^{1,2}

Although originally described as a nodal disorder, extranodal disease occurs in up to 40% of cases, with skin affected in about 10% of cases.^{1,3,4} More rarely, cutaneous lesions are the sole manifestation, with purely cutaneous-RDD (CRDD) representing a small minority (3%) of RDD described cases.^{1,3,4} CRDD is considered a distinct entity, based on the exclusive involvement of the skin, different demographic features and better prognosis, compared with systemic RDD.^{4,5}

As the cutaneous lesions are clinically nonspecific, the diagnosis of CRDD is histological, and essentially relying on the presence of an infiltrate containing large pale histiocytes, commonly displaying emperipolesis, accompanied by lymphocytes and abundant plasma cells. In the setting of no lymphadenopathy, the histopathological features of RDD are commonly misinterpreted, and it is important to consider that histological features vary in correlation with the cutaneous lesions duration.^{5,6}

CASE REPORT

A 53-year-old female presented with a 1 year-history of a poorly circumscribed, erythematous to brown, slightly verrucous, indurated 15cm plaque with superimposed violaceous papules and additional satellite erythematous papules, located on her left leg. The plaque progressed for 1 year, starting as a small, dark area, gradually enlarging (Figure 1). In addition, she had sparse dome-shaped erythematous papules located on her face and arms, which appeared two months before (Figure 2). The skin lesions were asymptomatic, and the general physical examination was unremarkable, with no lymphadenopathy, organomegaly, or systemic symptoms like fever, malaise or weight loss. Her past medical history included obesity, hypertension and bipolar disorder. The first clinical impression was Kaposi's sarcoma and skin biopsies were taken from her arm and leg.

Histological examination of a papule located on the arm that had evolved for approximately 2 months revealed a dense nodular infiltrate in the dermis, extending focally to the hypodermis. The infiltrate was mainly composed of large histiocytes with pale cytoplasm and variably sized vesicular nuclei, with large nucleoli, occasionally exhibiting intact inflammatory cells in their cytoplasm – emperipolesis (Figure 3). The histiocytic infiltrate was intermixed with plasma cells, lymphocytes and few neutrophils and eosino-

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phils. Lymphocytes tended to constitute aggregates within or at the periphery of the infiltrate (Figure 4).

The histological examination of the leg plaque, which had been present for 1 year, revealed a more superficial dense dermal infiltrate, composed by fewer histiocytes, and accompanied by a relatively higher number of lymphocytes, plasma cells, eosinophils and neutrophils. Emperipolesis was not identified, and there was moderate fibrosis surrounding the infiltrate (Figure 5). In both specimens, the histiocyte population was positive for S100 and CD68, but negative for CD1a, confirming the diagnosis of RDD (Figure 6).

Blood tests, including HIV1/2 and herpes virus 8, were normal or negative; and positive for IgG anti-Epstein-Bar virus and cytomegalovirus. A full-body CT scan excluded internal organ involvement and lymphadenopathy, and the patient was diagnosed with CRDD. Since the lesions were progressing and involved the face, thalidomide (300mg/d) was initiated. After 2 months, the leg plaque became flat, with no induration, leaving a residual, brownish discoloration. Lesions on the face and arms completely regressed with no pigmentary changes or scarring, and thalidomide was withdrawn.



FIGURE 1: Hyperpigmented, indurated plaque with superimposed and satellite papules on the left leg



FIGURE 2: Sparse, unspecific, erythematous papules on the arms and face

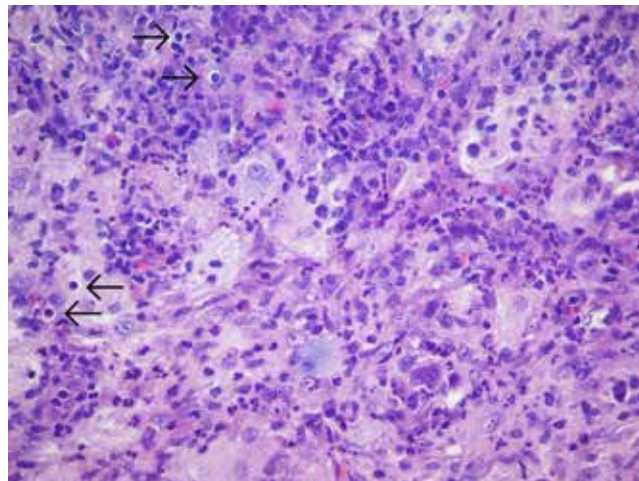


FIGURE 3: Emperipolesis- clear halos around intact cells within the cytoplasm of histiocytes. (H/E, original magnification x200)

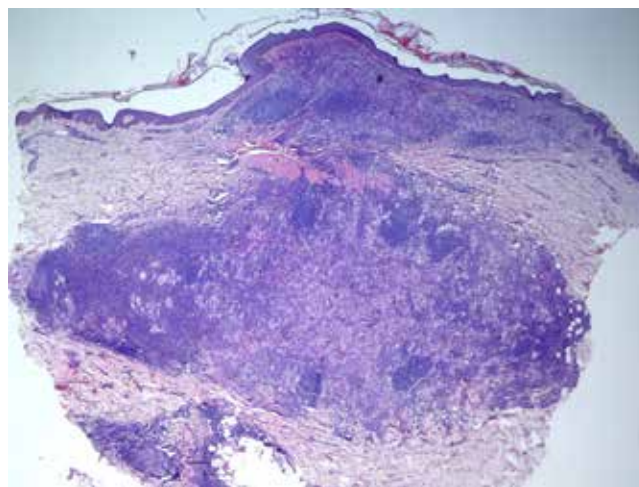


FIGURE 4: Dense, confluent population of large histiocytes with pale cytoplasm, located in the dermis and focally in the hypodermis; and nodular, lymphocytic aggregates within the infiltrate and at the periphery. (H/E, original magnification x25)

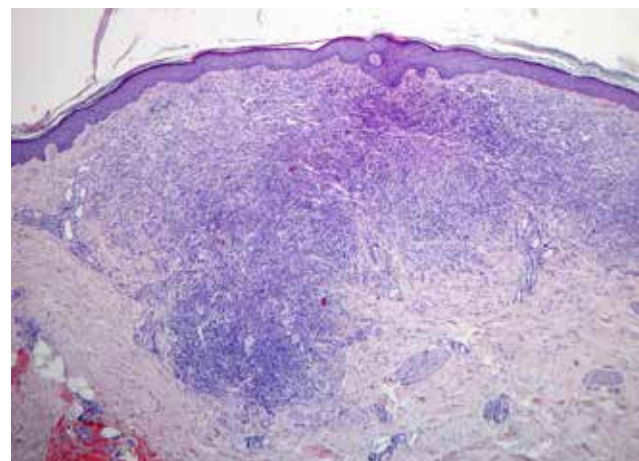


FIGURE 5: Dense, dermal infiltrate, presenting a triangular shape with its base oriented towards the surface, composed of fewer histiocytes; absence of emperipolesis and prominent fibrosis surrounding the infiltrate. (H/E, original magnification x40)

One year later, the patient noticed the recurrence of induration on the previous leg plaque and new satellite erythematous papules, which were biopsied 1 month after they appeared. The histopathological picture was superposable to what was previously found in the leg plaque; and in addition, suppurative foci were seen within the infiltrate of the new satellite papule, that also displayed increased vascularity, focal emperipolesis and perivenular extension of plasma cells (Figure 7). Since there was no recurrence in other body areas, we decided to treat the leg lesions with topical corticosteroids, with good response.

DISCUSSION

There are three main hypotheses for RDD etiology: i) an immune dysfunction induced by viral infection, namely HHV6, EBV or parvovirus B19. However, virus expression is inconsistently identified in nodal disease and has not yet been conclusively identified in CRDD; ii) RDD may be part of the spectrum of IgG4-related dis-

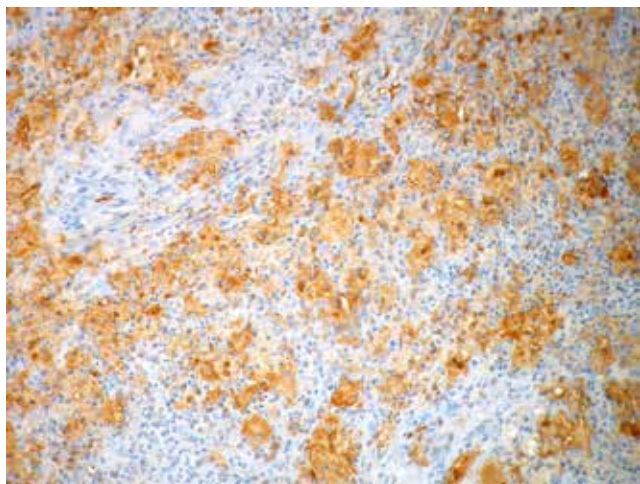


FIGURE 6: Diffuse anti-S100 cytoplasmic staining of histiocytic population. (S100 stain, original magnification x200)

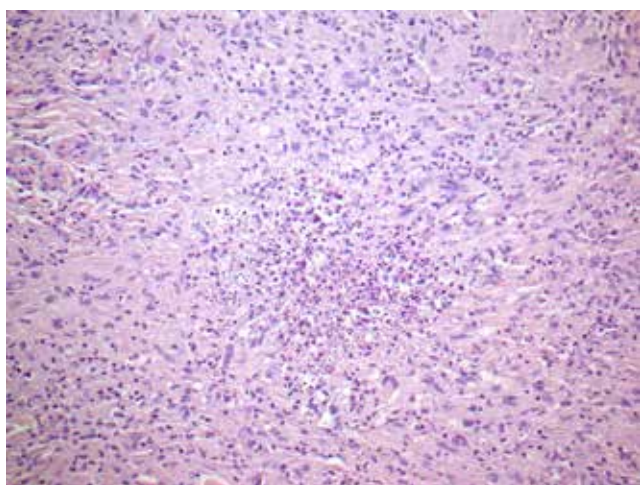


FIGURE 7: Suppurative foci within the histiocytic infiltrate, observed in a satellite papule of the leg lesion recurrence. (H/E, original magnification x100)

ease, based on recent reports and case series showing an increased number of IgG4 positive plasma cells.^{1,4,6,7,8,9} However, there is no clear evidence to support this hypothesis, and a large number of conditions outside the IgG4-related disease spectrum can be associated with an increased number of IgG4-positive plasma cells; iii) RDD may belong to a spectrum of disorders with SLC29A3 mutations, namely H syndrome.¹⁰ The evidence of a germline mutation in SLC29A3 in patients with familial RDD, as well as the finding of emperipolesis in cutaneous lesions of H syndrome would support this hypothesis, but this association has not been demonstrated in the cutaneous forms of the disease.^{10,11}

The classic clinical features described in CRDD were reproduced in our patient. Systemic RDD is more common in males and in children or young adults of African descent, whereas CRDD predominates in older females, of non-black ancestry.^{1,6,12} Rare fatalities can occur in systemic RDD, resulting from vital organ infiltration, progression to lymphoproliferative disorders, or the development of solid tumors. CRDD, contrarily, is typically self-limiting, does not require aggressive treatments, and it generally remains confined to the skin despite frequently running a recurrent course.^{5,4,12}

The cutaneous lesions can be protean (yellowish to reddish brown/violaceous macules, patches, plaques, nodules or tumors, pustules, acneiform, or transient panniculitis-like lesions), with a wide distribution (head and neck, trunk, upper and lower limbs, by decreasing order).^{1,4,6,7} Our patient exhibited a typical semiologic aspect of CRDD: a plaque, surrounded by satellite papules, and other clinical aspects commonly observed in CRDD, the multiplicity and combination of distinct lesions, and their tendency toward regression and recurrence.^{4,7} However, these clinical and evolutive features, albeit characteristic of CRDD, are seldom evocative of the diagnosis, which in this case was initially thought to be Kaposi's sarcoma. The absence of systemic/extracutaneous signs and symptoms, as documented in our patient, although essential for the diagnosis of CRDD, further rendered the clinical picture unspecific.²

It is the microscopic picture that allows the diagnosis. The histopathologic features of CRDD are akin to those found in the lymph nodes in systemic RDD.⁵ Typically, as featured in the arm lesion of our patient, a dermal/hypodermal infiltrate of large pale histiocytes exhibiting variable emperipolesis admixed with plasma cells, lymphocytes and occasional neutrophils and eosinophils is observed.^{4,5,7,12} However, this picture can change according to the age of the lesions: in early developing lesions, as found in the satellite papules of the recurrent leg lesion, collections of neutrophils and increased vascularity can be pronounced. On the other hand, in old/regressive lesions, as observed in the protracted leg plaque, emperipolesis may be absent, and surrounding fibrosis may be prominent, overshadowing the presence of histiocytic cells and hindering the diagnosis. In the absence of emperipolesis, the extension of plasma cells around thick wall venules and the peripheral arrangement of lymphoid aggregates, as observed in our case, are important clues for the histologic suspicion of CRDD.^{5,7}

The coexpression by the histiocytic CRDD cells of S-100 protein and monocyte/macrophage markers, such as lysozyme, α 1-antitrypsin, CD68 and CD163, the non-reactivity to Langerhans cell markers, including CD1 and langerin, which was also featured in

this case, is an important tool for diagnosis.^{1,2} Histologically, CRDD may be confused with other histiocytic proliferations. In reticulohistiocytosis, histiocytes have an eosinophilic ground glass cytoplasm and are most often S100 protein-negative. Langerhans cell histiocytosis can be distinguished from CRDD by the smaller size of the histiocytes, characteristic reniform folded nucleus, epidermotropism and positivity for CD1a and langerin. In juvenile xanthogranuloma, histiocytes are negative or only focally positive for S100 protein and, in contrast to CRDD, are positive for factor XIIIa. Eruptive xanthoma also lacks S100 protein immunoreactivity. It should be emphasized that in these histiocytic disorders, emperipolesis is not a feature.³ Nevertheless, although virtually diagnostic of RDD/CRDD in the appropriate clinical and pathologic setting, histiocytic emperipolesis is not unique to this condition. Emperipolesis can be found in examples of B-cell lymphomas and in the cutaneous lesions of the H syndrome, both easily discarded in our patient.^{3,11,13}

Furthermore, the pathologic findings allow to most of the clinical differential diagnoses for CRDD, including storage disorders, granulomatous diseases, histiocytic sarcoma, infections like mycobacteriosis and histoplasmosis, as well as Kaposi's sarcoma (in our case).²

The utility of a further workup in a patient with cutaneous RDD and no further systemic manifestations is not well-defined. As skin lesions can be the initial manifestation of systemic disease, we believe that CT-scans should be performed in patients presenting solely cutaneous lesions, to screen for visceral involvement.^{2,14}

Generally, CRDD has a benign course and is self-limiting, although patients may experience local relapse or persistent disease.⁶ Accordingly, therapy may be needed for cosmetic reasons and relapsing cases, as in our patient. Therapeutic options for CRDD are multiple, and due to the rarity of the condition, randomized trials are not available. Surgical excision remains the therapy of choice for solitary or small lesions.^{1,6} In addition, corticosteroids (the most widely used therapy in CRDD), thalidomide, interferon, cryosurgery, radiotherapy and chemotherapy have been assayed. In our patient (a hypertensive, obese, post-menopausal woman), thalidomide induced rapid remission, confirming previous reports^{4,7}, with positive aesthetic results with absence of facial residual changes.

We described a case of CRDD where emperipolesis was present only in recently developed lesions, but not found in older lesions, which instead revealed variable fibrosis surrounding a scantier histiocytic proliferation. Initial lesions additionally displayed neutrophil microabscesses and increased vascularity. Awareness of the histological aspects present in different lesions, which do not always contain the hallmark microscopic signs of CRDD, is particularly important to correctly diagnose this rare disorder. □

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